In the Specification:

Combination Use of Acetylcholinesterase Inhibitors and $GABA_A$ Inverse Agonists for the Treatment of Cognitive Disorders

This application claims priority from U.S. provisional application Serial No. 60/241,145, filed October 17, 2000, which is incorporated herein by reference in its entirety.

Background of the Invention

The present invention relates to the combination use of acetylcholinesterase (AchE) inhibitors and $GABA_A$ inverse agonists, which results in cognition enhancement. Such a combination is useful in treatment of disorders associated with cognition impairment including, but not limited to, Alzheimer's disease, mild cognitive impairment, age related cognitive decline, vascular dementia, Parkinson's disease, memory impairment associated with depression or anxiety, psychosis, Down's Syndrome, stroke, traumatic brain injury and attention deficit disorder.

Alzheimer's disease (AD) is characterized by a progressive loss of memory and inability to carry out normal activities of daily living and is frequently accompanied by changes in behavior and personality. Alzheimer's disease is associated with degeneration of cholinergic neurons, which play a fundamental role in cognitive functions. It is known that acetylcholinesterase inhibitors are effective in enhancing cholinergic activity and are useful in improving memory and function in Alzheimer's Disease patients. Rogers, S. L., Friedhoff, L. T., Apter, J. T., Richter, R. W., Hartford, J. T., Walshe, T. M., Baumel, B., Linden, R. D., Kinney, F. C., Doody, R. S., Borison, R. L. and Ahem, G. L., *The* Efficacy *and Safety of Donepezil in Patients with Alzheimer's Disease: Results of a US Multicentre, Randomized, Double-blind, Placebo-controlled Trial.* Dementia, 1996, volume 7, issue 6, pages 293-303. Rogers, S. L., Doody, R., Mohs, R. and Friedhoff, L. T., *E2020 Produces Both Clinical Global and Cognitive Test Improvement in Patients with Mild to Moderately Severe Alzheimer's Disease: Results of a 30 week Phase III Trial,* Neurology, 1996, volume 46, issue 2, Suppl. A217.

~~Modulators of the $GABA_A$ receptors are capable of enhancing cognition in rodent models of cognition. In such models, it has been demonstrated that a selective inverse agonist profile can lead to cognitive enhancers devoid of or with minimum proconvulsant, anxiogenic and stimulant activity. The $GABA_A$ inverse agonist binding and functional profile is described below:~~

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Table 1

Binding	Oocyte Functional Profile			
Ki Ro15-1788 Rat cortex	$\alpha1\beta2\gamma2$ EC_{50}/Efficacy	$\alpha2\beta3\gamma2$ EC_{50}/Efficacy	$\alpha3\beta3\gamma2$ EC_{50}/Efficacy	$\alpha5\beta3\gamma2$ EC_{50}/Efficacy
100 nM, preferably <30 nM	200 nM, preferably <150 nM/ <-10% or >+10%	Any*/>10%	Any*/>10%	200 nM, preferably <150 nM/ <-10%

*Though a wide range of EC_{50} values at the $\alpha2\beta3\gamma2$ and $\alpha3\beta3\gamma2$ subtype receptors is permitted, in practice the "Any/>10%" criteria are used for compounds having EC_{50} values at these subtypes below or equal to 100 times the EC_{50} values at the $\alpha1\beta2\gamma2$ and $\alpha5\beta3\gamma2$ subtype receptors. When the EC_{50} value of the compound at the $\alpha2\beta3\gamma2$ and $\alpha3\beta3\gamma2$ subtype receptor is more than 100 times greater than at the $\alpha1\beta2\gamma2$ and $\alpha5\beta3\gamma2$ subtype receptors then <10% in vitro efficacy would be acceptable.

A compound is identified as having cognitive enhancing potential when the EC_{50} value of the compound at the $\alpha1\beta2\gamma2$ and/or $\alpha5\beta3\gamma2$ subtype receptors is less than 200 nM, preferably less than 150 nM, and the efficacy measured is less than -5% or preferably less than -10%, and the efficacy measured at the $\alpha2\beta3\gamma2$ and $\alpha3\beta3\gamma2$ subtype receptors is greater than 5% or preferably greater than 10%. The combination of a $GABA_A$ cognitive enhancer and an AChE inhibitor results in greater (additive/synergistic) efficacy or cognitive/behavioral improvement in the treatment of the above disorders in comparison to the efficacy displayed by either agent alone. In addition, such a combination allows lower doses of each agent to be administered, resulting in efficacy similar to or greater than the one observed with higher doses of either agent alone, and reduced side effects (or higher therapeutic index).

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In the Summary of Invention

N-(2-Thienyl)methyl-6-dimethylamino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5 naphthyridine-3-carboxamide hydrochloride; and

N-[4-(Imidazolylmethy)lbenzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide,

or a prodrug thereof, or pharmaceutically acceptable salt or solvate of said compound or prodrug,

said composition being effective in the treatment of a cognitive disorder.

In a preferred embodiment, the $GABA_A$ inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

Non-limiting examples of acetylcholinesterase inhibitors include ~~Aricept~~ (donepezil, ~~E2020~~), ~~Exelon~~ (rivastigmine), metrifonate, galantamine, physostigmine, tacrine, huperzine A, and icopezil.

In a preferred embodiment, the acetylcholinesterase inhibitor is ~~Aricept~~ (donepezil, ~~E2020~~), or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

In a further preferred embodiment, the $GABA_A$ inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is ~~Aricept~~ (donepezil, ~~E2020~~) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

This invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier, a $GABA_A$ inverse agonist and an acetylcholinesterase inhibitor, wherein said $GABA_A$ inverse agonist compound is selected from a compound which is

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In a preferred embodiment, the acetylcholinesterase inhibitor is ~~Aricept~~ (donepezil, ~~E2020~~) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

In a further preferred embodiment, the $GABA_A$ inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

In a further preferred embodiment, the $GABA_A$ inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is ~~Aricept~~ (donepezil, ~~E2020~~) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

As used herein, the benefit of the combination treatment is obtained where treatment with a combination of a $GABA_A$ cognitive enhancer and an AChE inhibitor results in greater (either additive or synergistic) efficacy or cognitive/behavioral improvement in the treatment of a cognitive disorder, such as any of the above listed disorders, in comparison to the efficacy displayed by either agent alone. Such a combination preferably allows lower doses of each agent to be administered, resulting in efficacy similar to or greater than that observed with higher doses of either agent alone, and with reduced side effects (or higher therapeutic index). In a preferred embodiment, the combination treatment provides a synergistic therapeutic effect. In another preferred embodiment the combination treatment provides at least an additive effect with reduced side effects.

As used herein, a mammal in need of treatment of a cognitive disorder means a mammal, and preferably a human, that is suffering from, or is at risk of suffering from, a cognitive disorder.

As used herein, the terms "treat", "treating" and "treatment", and the like, as applied to cognitive disorders, refer to methods that slow, ameliorate, reduce or reverse such a disorder or any symptoms associated with said disorder, as currently afflicting the subject, as well as methods that prevent such a disorder or any symptoms thereof, from occurring.

The present invention further provides the use of a $GABA_A$ inverse agonist and an acetylcholinesterase

inhibitor in the manufacture of a medicament for treating a cognitive disorder. The $GABA_A$ inverse agonist and an acetylcholinesterase inhibitor may be combined in a single medicament or maintained in separate medicaments.

Non-limiting examples of acetylcholinesterase inhibitors include ~~Aricept~~ (donepezil, ~~E2020~~), ~~Exelon~~ (rivastigmine), metrifonate, galantamine, physostigmine, tacrine, huperzine A, and icopezil.

In a preferred embodiment, the acetylcholinesterase inhibitor is ~~Aricept~~ (donepezil, ~~E2020~~) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

In a further preferred embodiment, the $GABA_A$ inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

In a further preferred embodiment, the $GABA_A$ inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is ~~Aricept~~ (donepezil, ~~E2020~~) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

The present invention also provides a kit comprising:

a) a first compound being a $GABA_A$ inverse agonist as described above, and most preferably a compound of formula I, or an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt or solvate of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b) a second compound selected from the group consisting of an acetylcholinesterase inhibitor; and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c) a container for containing said first and second unit dosage forms wherein the amounts of said first and second compounds result in an enhanced therapeutic effect, as described above.

The kit may further comprise a printed label or a set of printed instructions directing the use of the pharmaceutical composition to treat a cognitive disorder.

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Detailed Description of the Invention

Modulators of the $GABA_A$ receptors are capable of enhancing cognition in rodent models of cognition. In such models, it has been demonstrated that a selective inverse agonist profile can lead to cognitive enhancers devoid of or with minimum proconvulsant, anxiogenic and stimulant activity. The $GABA_A$ inverse agonist binding and functional profile is described below:

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*Though a wide range of EC_{50} values at the $\alpha2\beta3\gamma2$ and $\alpha3\beta3\gamma2$ subtype receptors is permitted, in practice the "Any/>10%" criteria are used for compounds having EC_{50} values at these subtypes below or equal to 100 times the EC_{50} values at the $\alpha1\beta2\gamma2$ and $\alpha5\beta3\gamma2$ subtype receptors. When the EC_{50} value of the compound at the $\alpha2\beta3\gamma2$ and $\alpha3\beta3\gamma2$ subtype receptor is more than 100 times greater than at the $\alpha1\beta2\gamma2$ and $\alpha5\beta3\gamma2$ subtype receptors then <10% in vitro efficacy would be acceptable.

A compound is identified as having cognitive enhancing potential when the EC_{50} value of the compound at the $\alpha1\beta2\gamma2$ and/or $\alpha5\beta3\gamma2$ subtype receptors is less than 200 nM, preferably less than 150 nM, and the efficacy measured is less than –5% or preferably less than –10%, and the efficacy measured at the $\alpha2\beta3\gamma2$ and $\alpha3\beta3\gamma2$ subtype receptors is greater than 5% or preferably greater than 10%. The combination of a $GABA_A$ cognitive enhancer and an AChE inhibitor results in greater (additive/synergistic) efficacy or cognitive/behavioral improvement in the treatment of the above disorders in comparison to the efficacy displayed by either agent alone. In addition, such a combination allows lower doses of each agent to be administered, resulting in efficacy similar to or greater than the one observed with higher doses of either agent alone, and reduced side effects (or higher therapeutic index).

The $GABA_A$ ligands disclosed above may be prepared by the methods described in PCT publication WO 99/10347 by Neurogen Corporation, published March 4, 1999, which is incorporated herein by reference.

By lower alkyl in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

The amount and timing of compounds administered will, of course, be based on the judgment of the prescribing physician. Thus, because of patient-to-patient variability, the dosages given below are a guideline and the physician may titrate doses of the agent to achieve the activity that the physician considers appropriated for the individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as cognitive function, age of the patient, presence of preexisting disease, as well as presence of other disease (e.g., cardiovascular). The following paragraphs provide preferred dosage ranges for the various components of this invention (based on average human weight of 70 kg).

In general, an effective dosage for the $GABA_A$ is in the range of 0.001 to 30 mg/kg/day, preferably 0.01 to 10.0 mg/kg/day.

In general an effective dosage for the acetylcholinesterase inhibitor is in the range of 0.01 to 10 mg/kg/day. More specific dosages are as follows:
The specific dosages for the cholinesterase/butylcholinesterase inhibitors are as follows:

For donepezil ~~(Aricept™)~~ the range is 0.01 to 0.75 mg/kg/day.
For tacrine ~~(Cognex™)~~ the range is 0.1 to 2.3 mg/kg/day.
For rivastigmine ~~(Exelon™)~~ the range is 0.1 to 0.5 mg/kg/day.
For physostigmine ~~(Synapton)~~ the range is 0.01 to 0.4 mg/kg/day.
For galantamine ~~(Reminyl)~~ the range is 0.05 to 1.0 mg/kg/day.
For metrifonate ~~(Promem)~~ the range is 0.1 to 2.0 mg/kg/day.

It will be understood, however, that the specific dose level for any particular patient will depend up on a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions with a mullet-dose of the drug so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed or drinking water.

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Example 1

The following experiment demonstrates that sub-efficacious doses of Aricept and a compound of Formula I when used in combination attenuate a scopolamine-induced memory deficit in the spatial water maze task.

Method

Subjects: Animals used in these studies were naive male Sprague Dawley rats (SASCO St. Louis) weighing between 200-250 grams. Animals were housed in groups of three in a temperature (22°C ± 2°) and humidity (40-70% relative humidity) controlled vivarium with a 12-hour light/dark cycle. Animals had ad lib access to food and water.

Drugs: ~~Aricept~~ donepezil and said compound of Formula I were each dissolved in 50% polyethylene glycol (PEG), and scopolamine HCl (Sigma) was dissolved in 0.9% saline. ~~Aricept~~ donepezil and said compound of Formula I (alone or in combination) or 50% PEG was administered intravenously (IV) 5 minutes prior to scopolamine (0.125 mg/kg) or saline given intraperitoneally (IP). Training commenced 15 minutes after the IP injection.

Apparatus: The water maze apparatus consists of a circular tank (120 cm in diameter and 56 cm in height) with a black interior. The tank was filled with water (23°C) to a height of approximately 40 cm. Superimposed onto the tank were four quadrants (North, South, East and West). The tank was surrounded by external visual cues that consisted of a black and white checkered wall, a black and white striped wall, a blue wall, and a white wall. A stationary black circular Plexiglass platform with a black neoprene rubber top was placed in the northeast quadrant approximately 1cm below the surface of the water.

Procedure: An animal was initially placed on the platform in the tank for 20 seconds. Thereafter, the 6 trial acquisition training was begun by placing the rat in the water at the South entry position. The trial ended with the animal finding the platform or being placed onto it after 90 sec. Each of the subsequent five training trials was separated by an intertrial interval (ITI) of 2 minutes and was begun by placing the rat at different entry positions, the order of which was pseudo-randomized. One day after training, each drug-free animal was individually tested for retention on one trial. For each trial during acquisition and retention, a computerized video tracking system recorded the latency (sec) to reach the submerged platform, the total distance traveled (m) in the water maze, the number of zone (quadrant) transitions made, and the swim speed of the animal.